UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/827,023	04/19/2004	Bruce Blazar	46483-0096	2495

23973 7590 04/07/2009

DRINKER BIDDLE & REATH
ATTN: INTELLECTUAL PROPERTY GROUP
ONE LOGAN SQUARE
18TH AND CHERRY STREETS
PHILADELPHIA, PA 19103-6996

EXAMINER	
LI, QIAN JANICE	
ART UNIT	**PAPER NUMBER**
1633	

MAIL DATE	DELIVERY MODE
04/07/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/827,023	BLAZAR ET AL.	
	Examiner	Art Unit	
	Q. JANICE LI	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 January 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,7-11 and 28-36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,7-11 and 28-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The amendment and remarks submitted 1/5/09 are acknowledged. Claim 1 has been amended, claim 36 is newly added. Claims 1-5, 7-11, 28-36 are pending and under current examination.

Unless otherwise indicated, previous rejections that have been rendered moot in view of the amendment to pending claims and new grounds of rejections will not be reiterated. The arguments in 1/9/09 response would be addressed to the extent that they apply to current rejection.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2, 3, and 32 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, for reasons of record and following.

Claims 2 and 32 are vague and indefinite because it is unclear what positive step is encompassed by an isolation step "comprises a high level of stringency", and thus the metes and bounds of the claims are uncertain. Further, the specification does not provide a standard for ascertaining the requisite degree of the recited high stringency, and one of the skills in the art would not be reasonably apprised of the scope of the invention.

Claim 3 is vague and indefinite because of the claim recitation "wherein isolation step further comprises substantially enhancing CD4+CD25^{bright} cells in said isolated population, while substantially depleting CD25^{dim} cells in said isolated population". It is unclear what steps and means the claim encompasses, and hence the metes and bounds of the claims are uncertain.

The applicant argues that patent law allows the inventor to be his own lexicographer, the specification as filed recites the phrase, and the specification describes the double column purification procedure is useful in view of the fact of that CD25bright subset of CD4+CD25+ cells have greater suppressor activity.

The argument has been fully considered but found not persuasive. This is because although the specification states, "`"stringent purification" is emphasized (preferably two cycles of selection, and extensive washing)`", the claims are vague because as noted in MPEP § 2111, claims must, under modern claim practice, stand alone to define invention. It is not proper to read limitations appearing in the specification into the claim when these limitations are not recited in the claim. See In re Paulsen, 30 F.3d 1475, 1480, 31 USPQ2d 1671 (Fed. Cir. 1994); Intervet America Inc. v Kee-Vet Lab. Inc., 887 F.2d 1050, 1053, 12 USP2d 1474, 1476 (Fed. Cir. 1989). In the instant case, the recitation "comprises a high level of stringency", or "substantially enhance" does not make clear what step(s) are embraced by the recitation. If they refer to multiple cycles of selection and extensive wash, such steps should be positively identified in the claims.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5, 7-11, 28-36 stand or newly rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for

providing human T regulatory (Treg) cells with *enhanced suppressor activity* under the conditions now claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims, for reasons of record and following.

Applicant's arguments filed 1/9/09 have been fully considered but they are not persuasive.

With respect to *Baecher-Allan,* the applicant argues that instant claims are directed to using immobilized anti-CD28 antibody whereas *Baecher-Allan* uses soluble anti-CD28 antibody.

In response, it appears the two antibodies differ only in their physical forms, i.e. in a solution or immobilized. However, since they both recognize the same molecule CD28, the effect generated should be the same upon contacting CD4+CD25+ cells. Accordingly, the argument is not persuasive in the absence of clear and convincing evidence to the contrary.

The applicant then argues that instant discovery relies on stringently purify CD4+CD25+ suppressor cells.

In response, it is noted claim 1 does not require the stringency. As to the stringency, the purity of CD4+CD25+ cells taught by *Baecher-Allan* were sorted for CD4+ $CD25^{high}$ using FACSVantage, and such technique routinely obtain 90-95% purity.

The applicant fails to address the following rejection set forth in the Office action mailed 7/11/08.

Furthermore, it appears, in the specification, all of the experimental data were obtained by expanding Treg cells at the anti-CD3/CD28 ratio at 1:1 because the specification cited *Levine et al* for experimental protocol, who uses the anti-CD3/CD28 ratio at 1:1, and the specification uses the commercially available Dynabeads CD3/CD28 expander (Specification, paragraph 0026 and example 8), which was coated at ratio 1:1 (see Dynabeads datasheet). Accordingly, the specification fails to provide sufficient evidence to contradict what was known in the art at the time, and fails to support what is now claimed.

Accordingly, for reasons of record and *supra*, the rejection stands.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-5, 7-11, 28-35 stand rejected and claim 36 is newly rejected under 35 U.S.C. 103(a) as being unpatentable over *Schuler et al*. (US 2005/0101012 A1), in view of *Baecher-Allan et al.* (J Immunol 2001; 167:1245-530, IDS) and CD25 Microbeads Datasheet (Miltenyi, publicly available at least on Nov. 1996 as evidenced by *Elkord*, Biocompare Review, 1996).

Schuler teaches a method for generating human T regulatory cells, the method comprises contacting a sample of human CD4+ T cells with anti-CD25 antibody to produce an isolated population of human CD4+CD25+ Treg cells (see e.g. fig. 1A); *Schuler* also teaches expanding CD4+CD25+ Treg cells *ex vivo* in the presence of stimulation agents, wherein anti-CD3 and anti-CD28 antibodies are on top of the list (e.g. paragraph 0035-0036). *Schuler* teaches, similar to their murine counterparts, the human CD4+CD25+ T cells showed almost no proliferation upon polyclonal activation by plate-bound anti-CD3/anti CD28, but when combined with IL-2, the proliferation was significantly enhanced (col 2, page 4, and fig 2). Fig. 2D shows increased production of CD4+CD25+ Treg cells in the presence of IL-2, IL-15. *Schuler* teach the positive selection through MACS-sorted process provides a more than 95% pure population of CD4+CD25+ cells (Specification, paragraph 0081), and thus the isolation step meets a high level stringency standard.

Although *Schuler* uses immobilized anti-CD3 and soluble anti-CD28, apparently the plate-bound anti-CD3/CD28 was known in the art as mentioned by *Schuler*, and appears to fall within the bounds of experimental preference and optimization, the two means do not appear to be patentably distinct.

The claims are directed to adjusting cell numbers:beads volume ratio to enhancing CD4+CD25^{bright} cells in the isolated cell population and multiple rounds of magnetic column separation and elution. Although *Schuler* in view of *Baecher-Allan* do not teach these technical details, these were knowledge known in the art as disclosed in the CD25 MicroBeads Datasheet, wherein the manufacture teaches adjusting cell/beads ratio for different purpose (e.g. the table in § 2.2), and multiple rounds of column separation and elution (see the protocol in § 2.3.

As to the direct and indirect antibody conjugation, the technique was well established in the art. While the CD25 may well be directly conjugated to the beads through magnetic sorting process as used by *Schuler*, *Schuler* as well as *Baecher-Allan* (column 2, page 1246) also teaches toxin-, FITC- or PE-conjugated antibodies (Specification, paragraph 0045, 0048). Accordingly, these limitations fall within bounds of experimental preference and optimization.

Schuler differs from instantly claimed method in that they used the anti-CD3 and anti-CD28 at a ratio that equals to one, not less than one; and *Schuler* did not distinguish CD25 bright or dim population.

Baecher-Allan supplemented the deficiency by establishing it was known in the art that CD25 population could further divided into bright (high) and dim (low), and *Baecher-Allan* use the CD+CD25^{high} population for the suppressor functional test (e.g. figures 1-3). *Baecher-Allan* supplemented the deficiency by establishing it was also well known in the art when the antibodies were at a ratio 1:10 (less than 1:5), the suppressor function is significantly higher compared to ratio 1:1 (figure 2, bottom row).

New claim 36 recites "wherein the isolated population of human CD4+CD25+ Treg cells are cultured in the presence of a CD4+ feeder layer or CD4+ feeder layer conditioned medium".

Baecher-Allan teaches culturing CD4+CD25+ Treg cells in direct contact with CD4+ cells or in the form of upper and lower chamber in a transwell culture (CD4+ conditioned medium, see figure 5).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method taught by *Schuler* with that of *Baecher-Allan* by using anti-CD3 and anti-CD28 at a ratio of less than one and following through the manufacture's protocol for isolating CD4+CD25+ cell population, adjusting the cell/beads ratio for different purpose, or further culturing CD4+CD25+ cells in the presence of a CD4+ cell layer with a reasonable expectation of success. Accordingly, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Response to Arguments

In the remarks, the applicant stated that they have amended claim 1 to recite isolated cells are further cultured in the presence of a CD4+ feeder layer.

In response, the amended claim 1 of record does not contain the limitation. Further the co-culture as taught by *Baecher-Allan* was embraced by the limitation as recited in claim 36. Accordingly, the rejection stands.

Claim 36 is also newly rejected under 35 U.S.C. 103(a) as being unpatentable over *Schuler et al.* (US 2005/0101012 A1), in view of *Baecher-Allan et al.* (J Immunol 2001; 167:1245-530, IDS) and CD25 Microbeads Datasheet (Miltenyi, publicly available at least on Nov. 1996 as evidenced by *Elkord*, Biocompare Review, 1996), further in view of *Levings et al.* (J Exp Med 2001;193:1295-1301, IDS).

Schuler et al. in view of *Baecher-Allan et al.* teaches using a T cell-stimulating agent or antigen-presenting cells for Treg cell expansion, not CD4+ cells.

Levings et al. supplemented the deficiency by establishing it was well known in the art to use other cell types for stimulating CD4+CD25+ cell growth. *Levings et al.* teaches co-culture isolated CD4+CD25+ cells with PBMC, which contains CD4+ cells .

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method taught by *Schuler* in view of *Baecher-Allan* by co-culturing CD4+CD25+ cells with PBMC comprising CD4+ cells as taught by *Levings* with a reasonable expectation of success. Given numerous cell types known in the art for stimulating Treg cell, the limitation falls within the bound of experimental preference and optimization. Accordingly, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Q. JANICE LI** whose telephone number is **571-272-0730**. The examiner can normally be reached on 9 AM -7:00pm, Monday through Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joseph Woitach** can be reached on **571-272-0739**. The **fax** numbers for the organization where this application or proceeding is assigned are **571-273-8300**.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

For all other customer support, please call the USPTO Call Center (UCC) at **800-786-9199**.

/Q. JANICE LI/
Primary Examiner, Art Unit 1633